Brahma is required for cell cycle arrest and late muscle gene expression during skeletal myogenesis.

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Public Summary:
Adult skeletal muscle regeneration relies on quiescent myogenic stem cells associated with myofibers, termed satellite cells. In response to injury, they became activated, entering cell cycle, leading to two possible outcomes: myogenic progenitor cells that differentiate to repair damaged muscle fibers and, a minor population of precursor cells that returns to its quiescence stage, replenishing the satellite cell compartment as a self-renewal process. Our recent studies Brg1 and Brm, the two catalytic sub-units of the ATP-dependent SWI/SNF chromatin-remodeling complex, have distinct functions at specific stages of skeletal myogenesis. In particular, we have discovered that Brm is essential for cell cycle arrest in satellite cells, via repression of the G1-S phase cell cycle activator Cyclin D1. Satellite cells from Brm null mice show an intrinsic defect in cell cycle regulation and differentiation ability, consisting of impaired cell cycle arrest and defective formation of multinucleated myofibers. Consistently, Brm null mice displayed impaired muscle regeneration ability after injury, with an aberrant proliferation of satellite cells and delayed formation of new myofibers. Interestingly, we have observed a low frequency number of EdU-positive Pax7-satellite cells in unperturbed muscles of Brm null mice, suggests that Brm deficiency might also alter satellite cell quiescence and self-renew properties. Together, our results indicate that Brm-containing SWI/SNF complex is a key regulator of adult muscle stem cells.

Scientific Abstract:
Although the two catalytic subunits of the SWI/SNF chromatin-remodeling complex--Brahma (Brm) and Brg1--are almost invariably co-expressed, their mutually exclusive incorporation into distinct SWI/SNF complexes predicts that Brg1- and Brm-based SWI/SNF complexes execute specific functions. Here, we show that Brg1 and Brm have distinct functions at discrete stages of muscle differentiation. While Brg1 is required for the activation of muscle gene transcription at early stages of differentiation, Brm is required for Ccnd1 repression and cell cycle arrest prior to the activation of muscle genes. Ccnd1 knockdown rescues the ability to exit the cell cycle in Brm-deficient myoblasts, but does not recover terminal differentiation, revealing a previously unrecognized role of Brm in the activation of late muscle gene expression independent from the control of cell cycle. Consistently, Brm null mice displayed impaired muscle regeneration after injury, with aberrant proliferation of satellite cells and delayed formation of new myofibers. These data reveal stage-specific roles of Brm during skeletal myogenesis, via formation of repressive and activatory SWI/SNF complexes.